

08-10-00

H

Attorney Docket No. PHO-113

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT APPLICATION TRANSMITTAL LETTER

Transmitted herewith for filing is the patent application of:

1. Inventor(s): H. Craig Dees, Timothy C. Scott, John T. Smolik, Eric A. Wachter and Walter G. Fisher
2. Title: Improved Topical Medicaments And Methods For Photodynamic Treatment Of Disease

Name of applicant(s) and current correspondence address of applicant(s)

Name: H. Craig Dees  
Citizenship: USA  
Residence and  
Mailing Address: 1006 Wyndham Way, Apt. 1517, Knoxville, Tennessee 37923

Name: Timothy C. Scott  
Citizenship: USA  
Residence and  
Mailing Address: 10225 Bob Gray Road, Knoxville, Tennessee 37923

Name: John Smolik  
Citizenship: USA  
Residence and  
Mailing Address: 119 Tanasi Court, Loudon, Tennessee 37774

Name: Eric A. Wachter  
Citizenship: USA  
Residence and  
Mailing Address: 138 Bay Path Drive, Oak Ridge, Tennessee 37830

Name: Walter G. Fisher  
Citizenship: USA  
Residence and  
Mailing Address: 2009 Still Water Lane, Knoxville, Tennessee 37922

00/60/80  
JC853 U.S. PTO

JC857 U.S. PTO  
09/635276

08/09/00

Enclosed are:

<u>  X  </u>	<u>  2  </u> Sheets of Drawings
<u>  X  </u>	Formal
<u>      </u>	Informal
<u>      </u>	Assignment of invention to <u>Photogen, Inc.</u>
<u>  X  </u>	<u> 20 </u> Pages of Specification
<u>  X  </u>	<u>  7  </u> Pages of Claims
<u>  X  </u>	Abstract of The Disclosure
<u>  X  </u>	Title Page
<u>      </u>	Statement of Small Entity
<u>      </u>	Declaration and Power of Attorney
<u>      </u>	Information Disclosure Statement
<u>  X  </u>	Appointment of Associate Attorneys

This application claims the benefit of U.S. Provisional Application(s) No(s).: 60/149,015 filed August 13, 1999 which is a continuation-in-part of USSN 08/989,231, filed December 11, 1997, USSN 09/130,041, filed on August 6, 1998, USSN 09/184,388, filed on November 2, 1998, and USSN 09/216,787, filed on December 21, 1998.

**Claims as Filed**

	Number Filed		Number Extra	Rate	Fee
Total	37	-20	17	(small entity) x 9 (others) x 18	\$306.00
Independent	7	-3	4	(small entity) x 39 (others) x 78	\$312.00
Multiple Dependent	0	0	0	(small entity) x 130 (others) x 260	\$0.00
Basic Fee				(small entity) x 345 (others) x 690	\$690.00
Assignment					\$0.00
Total Fee					\$1308.00

\_\_\_\_\_ Please charge my Deposit Account No. 50/1039 in the amount of \$ \_\_\_\_\_. A duplicate copy of this sheet is enclosed.

X The Commissioner is hereby authorized to charge any additional fees (except the issue fee) which may be required at any time during the prosecution of this application without specific authorization, or credit any overpayment to Deposit Account No. 50/1039. A duplicate copy of this sheet is enclosed.


X A check in the amount of \$ 1308 is enclosed to cover the filing fee and the recordation of the Assignment, if any, transmitted herewith.

Date: August 9, 2000

"Express Mail" Mailing Label No. EL613562139

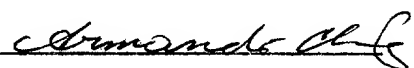
Date of Deposit August 9, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

  
 Mark J. Murphy  
 Registration No. 34,225  
 COOK, ALEX, MCFARRON, MANZO,  
 CUMMINGS & MEHLER, LTD.  
 200 West Adams St.  
 Suite 2850  
 Chicago, Illinois 60606  
 (312) 236-8500

- 3 -

Name ARMANDO CHING  
 (typed or printed)

Signature 

"Express Mail" Mailing Label No. EL613562139

Date of Deposit August 9, 2000

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Name ARMANDO CHING  
(typed or printed)

Signature Armando Ching

**IMPROVED TOPICAL MEDICAMENTS AND METHODS FOR  
PHOTODYNAMIC TREATMENT OF DISEASE**

Inventors: H. Craig Dees, Timothy C. Scott, John T. Smolik, Eric A. Wachter and Walter G. Fisher

## **BACKGROUND OF THE INVENTION**

This application claims the benefit of U.S. Provisional Application No. 60/149,015 filed August 13, 1999 which is a continuation-in-part of USSN 08/989,231, filed December 11, 1997, USSN 09/130,041, filed on August 6, 1998, USSN 09/184,388, filed on November 2, 1998, and USSN 09/216,787, filed on December 21, 1998, which are herein incorporated by reference in their entirety.

The present invention is related to certain photodynamic, topically-applicable medicaments and methods for treatment of human or animal tissue using photodynamic therapy (PDT).

PDT was originally developed to treat cancer and other diseases with the promise of limiting the invasiveness of the therapeutic intervention and lessening potential collateral damage to normal, non-diseased tissue. In its simplest form, PDT is the combination of a photosensitive agent with special forms of illumination to produce a therapeutic response in certain tissues, such as a tumor. The agent attains an excited, active state when it absorbs one or more photons and then is or becomes efficacious. Key elements of a successful PDT regimen include either selective application or selective uptake of a photosensitive agent into the diseased tissue and site-specific application of the activating light. PDT agents are typically applied systemically (for example, via intravenous injection or oral administration) or via localized topical application directly to diseased tissues (for example, via topical creams, ointments, or sprays). Subsequent to administration of the agent (typically 30 minutes to 72 hours later), an activating light is applied to the disease site, locally activating the agent, and destroying the diseased tissue. Light is typically applied by direct illumination of the site, or by delivery of light energy to internal locations using a fiberoptic catheter or similar device.

Most current PDT regimens are based on systemic application of porphyrin-based agents or topical or systemic application of psoralen-based agents. Examples of porphyrin-based agents include porfimer sodium (PHOTOFRIN®), hematoporphyrin-derivative (HPD), benzoporphyrin derivative

(BPD), Lutex, BOPP, 5-aminolevulinic acid (ALA), and SnET<sub>2</sub>. PHOTOFRIN® is one of the few agents currently licensed by the U.S. FDA. Porphyrin-based agents generally are derived from complex mixtures of natural or synthetically prepared materials, and may contain components that are lipophilic. As a possible result of this lipophilicity, porphyrin-based agents have shown a slight  
5 tendency to preferentially accumulate in some tumors and other diseased tissues. However, the targeting of such agents to diseased tissue is still unacceptably low when compared to uptake in normal tissue (i.e., at most 2-10x greater uptake in diseased tissue relative to normal tissue). The psoralens, such as 8-MOP, 5-MOP, trioxsalen, and AMT, are nucleic acid intercalators that function by impairing cellular physiology. This intercalation appears to be relatively indiscriminate in terms  
10 of tissue type, and as a result these agents also exhibit minimal specificity for diseased tissue. Thus, current agents have failed to exhibit sufficient specificity, and may exhibit additional disadvantages, including persistent systemic or localized photosensitivity, systemic or localized toxicity, and unacceptable treatment cost (due to high agent cost or excessive dosage requirements).

The inherent disadvantages of various current PDT agents and medicaments containing such  
15 agents have made acceptable PDT-based treatment of various human and animal conditions difficult or impossible. These disadvantages are particularly serious in the case of indications affecting external or internal surface or near surface tissues, where it would be desirable to have medicaments suitable for localized, selective treatment of the desired tissues. Such indications include a variety of conditions affecting the skin and related organs, the mouth and digestive tract and related organs, the  
20 urinary and reproductive tracts and related organs, the respiratory tract and related organs, as well as various other tissue surfaces, such as tissue surfaces exposed during surgery.

Therefore, it is an object of the present invention to provide new medicaments, medical uses for such medicaments based on targeted application of such medicaments and methods for treatment

using such medicaments, thereby resulting in increased efficacy and safety and reduced cost of treatment.

### **SUMMARY OF THE PRESENT INVENTION**

5           The present invention is directed to new photodynamic, topically-applicable medicaments and certain medical uses of such photodynamic medicaments or methods for treatment using such medicaments for treatment of human or animal tissue, wherein a primary active component of such medicaments is a halogenated xanthene, and more preferably Rose Bengal or its derivative. The halogenated xanthenes constitute a family of potent photosensitizers that become photoactivated  
10 upon illumination with visible wavelengths of light. Such medicaments can also be called pharmaceutical compositions or agents.

          The inventors of the present invention have found that such medicaments are useful for treatment of a variety of conditions affecting the skin and related organs, the mouth and digestive tract and related organs, the urinary and reproductive tracts and related organs, the respiratory tract and related organs, as well as various other tissue surfaces, such as tissue surfaces exposed during  
15 surgery. These medicaments are applied in various formulations including liquid, semisolid or aerosol delivery vehicles. Photoactivation of photoactive ingredients in such medicaments produces a desirable medical response, such as destruction of microbial infection, reduction or elimination of tissue irritation, reduction or elimination of hyperproliferative tissue, reduction or elimination of cancerous or precancerous tissue, reduction or elimination of surface or subsurface lipocytes or lipid  
20 deposits, and many other similar indications.

          In a preferred embodiment, such medicaments are used for treatment of a variety of conditions affecting the skin and related organs.

In another preferred embodiment, such medicaments are used for treatment of a variety of conditions affecting the mouth and digestive tract and related organs.

In another preferred embodiment, such medicaments are used for treatment of a variety of conditions affecting the urinary and reproductive tracts and related organs.

5 In another preferred embodiment, such medicaments are used for treatment of a variety of conditions affecting the respiratory tract and related organs.

In another preferred embodiment, such medicaments are used for treatment of a variety of conditions affecting various other internal or external tissue surfaces, such as tissue surfaces exposed during surgery.

10 In another preferred embodiment, such medicaments are used for treatment of a variety of conditions related to microbial or parasitic infection.

In another preferred embodiment, such medicaments are produced in various formulations including liquid, semisolid or aerosol delivery vehicles.

## 15 **BRIEF DESCRIPTION OF THE DRAWINGS**

In describing the preferred embodiments, reference is made to the accompanying drawings wherein:

FIGURE 1(a) shows the generalized chemical structure of the halogenated xanthenes.

FIGURE 1(b) shows the chemical structure of Rose Bengal.

20 FIGURE 2 shows example absorbance spectra of several halogenated xanthenes.



## DETAILED DESCRIPTION OF THE PRESENTLY PREFERRED EMBODIMENTS

The present invention is directed to new photodynamic, topically-applicable medicaments and certain medical uses of such photodynamic medicaments or methods for treatment using such medicaments for treatment of human or animal tissue, wherein a primary active component of such medicaments is a halogenated xanthene. Such halogenated xanthenes discussed *infra* are capable of exhibiting a desirable photodynamic effect when applied to or otherwise delivered to certain human or animal tissues, and undergo photodynamic activation in such tissues upon illumination with visible, and in particular green, light. These desirable effects include reduction or elimination of disease or other undesirable conditions, including eradication of cancerous or pre-cancerous tumors and infectious agents, and are applicable to a variety of conditions affecting the skin and related organs, the mouth and digestive tract and related organs, the urinary and reproductive tracts and related organs, the respiratory tract and related organs, and various other internal or external tissue surfaces, such as tissue surfaces exposed during surgery.

In a preferred embodiment, such medicaments are produced in various formulations including liquid, semisolid or aerosol delivery vehicles.

### 1. Properties of the preferred photoactive components and medicament formulations.

The applicants have discovered that a certain class of photoactive agents are broadly applicable for producing topically-applicable medicaments for treatment of certain human and animal tissues. These photoactive agents are referred to as halogenated xanthenes and are illustrated in Figure 1a, where the symbols X, Y, and Z represent various elements present at the designated positions, and the symbols R<sup>1</sup> and R<sup>2</sup> represent various functionalities present at the designated positions.

Selected chemical and physical properties (such as the chemical constituents at positions X, Y, and Z and the functionalities R<sup>1</sup> and R<sup>2</sup>, along with molecular weight and photochemical characteristics) of representative halogenated xanthenes are summarized in attached Table 1. The general properties of this class of agents are discussed in further detail in USSN 09/130,041, filed on August 6, 1998, USSN 09/184,388, filed on November 2, 1998, and USSN 09/216,787, filed on December 21, 1998, which are herein incorporated by reference in their entirety. In general, the halogenated xanthenes are characterized by a low dark cytotoxicity (toxicity to cells or tissues in the absence of photoactivation), high light cytotoxicity (toxicity to cells or tissues upon photoactivation) and chemical and photochemical properties that are substantially unaffected by the local chemical environment or the attachment of functional derivatives at positions R<sup>1</sup> and R<sup>2</sup>. This makes such chemical agents, and in particular medicaments formulated from such agents, excellent PDT agents for the treatment of human and animal tissues.

It is thus a preferred embodiment of the present invention that a topically-applicable medicament be produced that contains, as an active ingredient at a concentration of from greater than approximately 0.001% to less than approximately 20%, at least one halogenated xanthene.

It is further preferred that this medicament include the halogenated xanthene Rose Bengal (4,5,6,7-tetrachloro-2',4',5',7'-tetraiodofluorescein, illustrated in Figure 1b).

Other example halogenated xanthenes that can be used in the present invention include, but are not limited to, one or more of: Fluorescein; 4',5'-Dichlorofluorescein; 2',7'-Dichlorofluorescein; 4,5,6,7-Tetrachlorofluorescein; 2',4',5',7'-Tetrachlorofluorescein; Dibromofluorescein; Solvent Red 72; Diiodofluorescein; Eosin B; Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or

Trichloroerythrosin; Mono-, Di-, or Tricfluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein.

Further, as evidenced by the data shown in Table 1 and in Figure 2, it is clear that the halogenated xanthenes share common spectroscopic properties, including a high single-photon cross-section extending from approximately 500 nm to 600 nm. These properties are substantially invariant regardless of state of derivatization (for example, at positions R<sup>1</sup> and R<sup>2</sup>) or of chemical or biological environment. This feature facilitates photoactivation with commonly available visible light sources, such as cw or pulsed lasers or lamps, operating in the band from approximately 500 nm to 600 nm, and circumvents the need to substantively change sources if the specific photoactive component of the medicament is varied or modified, as disclosed herein. Furthermore, the inventors of the present invention have shown that the halogenated xanthenes are capable of being activated using non-linear, multi-photon excitation under certain conditions when using light in the near infrared band from approximately 700 nm to 1200 nm (using methods, such as for example, those taught in USSN 08/989,231, filed December 11, 1997 and USSN 09/096,832 filed June 12, 1998, which are incorporated herein by reference). Such excitation methods provide additional utility in activation of medicaments formulated from such agents, such as for example when it is desirable to increase the depth of photoactivation to positions substantially below an exposed tissue surface.

As an example of these desirable chemical, biochemical, and physical properties, the inventors have found that the prototypical halogenated xanthene, Rose Bengal, will accumulate preferentially in (i.e. target) some tumors and other diseased tissues and pathogens, has negligible dark cytotoxicity, high light cytotoxicity upon illumination with visible light, relatively low cost, and the ability to clear rapidly from the body.

Moreover, the inventors have discovered that the facility with which the halogenated xanthenes target specific tissues or other sites can be further optimized by attachment of specific functional derivatives at positions  $R^1$  and  $R^2$ , so as to change the chemical partitioning or biological activity of the agent. For example, attachment of one targeting moiety or more at positions  $R^1$  or  $R^2$  can be used to improve targeting to specific tissues, such as cancerous tumor tissues or sites of localized infection. An example of this is esterification at position  $R^1$  with a short aliphatic alcohol, such as n-hexanol, to produce a derivatized agent exhibiting enhanced partitioning into lipid-rich tumor tissues.

It is thus a further preferred embodiment that at least one of the at least one halogenated xanthene active ingredients includes at least one targeting moiety selected from a group that includes DNA, RNA, amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors or complexing agents, lipid receptors or complexing agents, protein receptors or complexing agents, chelators, encapsulating vehicles, short- or long-chain aliphatic or aromatic hydrocarbons, including those containing aldehydes, ketones, alcohols, esters, amides, amines, nitriles, azides, or other hydrophilic or hydrophobic moieties. A further example of this embodiment is derivatization of Rose Bengal with a lipid (at position  $R^1$ , via esterification), so as to increase the lipophilicity of Rose Bengal, and thereby modify its targeting properties in a patient.

Because the halogenated xanthenes and their derivatives are, in general, solids in their pure form, it is preferred that, for proper delivery to desired tissues, such agents be formulated in appropriate delivery vehicles. Approaches to such formulation will be generally known to those of ordinary skill in the art. Specifically, such formulations are preferred so as to facilitate agent contact with, and delivery to, desired tissues to be treated.

It is thus a further preferred embodiment of the present invention that at least one halogenated xanthene or halogenated xanthene derivative be formulated as a medicament in a topically-applicable

form, such as in a liquid, semisolid, solid or aerosol delivery vehicle, including aqueous, non-aqueous or nanoparticulate suspensions, solutions, creams, ointments, gels, syrups, suppositories or micro-droplet sprays. The at least one halogenated xanthene or halogenated xanthene derivative may be dissolved or suspended in such delivery vehicle, wherein this vehicle may, in addition to the at least one halogenated xanthene or halogenated xanthene derivative, include various builders, stabilizers, emulsifiers or dispersants, preservatives, buffers, electrolytes, and tissue penetrating or softening agents. Such components of the delivery vehicle may be present as the primary component (by weight or volume) of the medicament, or as a minor component that serves in an adjuvant role in agent delivery.

For example, appropriate builders include cellulose and cellulose derivatives, such as starch, and alginates.

Examples of appropriate stabilizers, emulsifiers or dispersants include liposomes, nanoparticulates and nanodispersions, microparticulates and microdispersions, as well as various lipids, detergents and other surfactants.

Examples of appropriate preservatives include benzalkonium chloride, thimerosal, and urea.

Examples of appropriate buffers include monobasic or dibasic phosphate salts, citrate salts, bicarbonate salts, and ethanolamine.

Examples of appropriate electrolytes include sodium, potassium, calcium and magnesium chlorides, phosphates, and nitrates.

Examples of appropriate tissue penetrating, softening or solvating agents and adjuvants include:

- various sulfoxides, such as DMSO and decylmethylsulfoxide;

- various aliphatic and fatty alcohols, such as ethanol, propanol, hexanol, octanol, benzyl alcohol, decyl alcohol, lauryl alcohol, and stearyl alcohol;
- various linear and branched, saturated and unsaturated fatty acids, such as lauric acid, caproic acid, capric acid, acid, myristic acid, stearic acid, oleic acid, isovaleric acid, neopentanoic acid, trimethyl hexanoic acid, neodecanoic acid and isostearic acid;
- various aliphatic and alkyl fatty acid esters, including isopropyl n-butyrate, isopropyl n-hexanoate, isopropyl n-decanoate, isopropyl myristate, isopropyl palmitate, octyldodecyl myristate, ethyl acetate, butyl acetate, methyl acetate, methylvalerate, methylpropionate, diethyl sebacate and ethyl oleate;
- various polyols, such as propylene glycol, polyethylene glycol, ethylene glycol, diethylene glycol, triethylene glycol, dipropylene glycol, glycerol, propanediol, butanediol, pentanediol and hexanetriol;
- various amides, such as urea, dimethylacetamide, diethyltoluamide, dimethylformamide, dimethyloctamide, dimethyldecamide; biodegradable cyclic urea, such as 1-alkyl-4-imidazolin-2-one; pyrrolidone derivatives, such as 1-methyl-2-pyrrolidone, 2-pyrrolidone, 1-lauryl-2-pyrrolidone, 1-methyl-4-carboxy-2-pyrrolidone, 1-hexyl-4-carboxy-2-pyrrolidone, 1-lauryl-4-carboxy-2-pyrrolidone, 1-methyl-4-methoxycarbonyl-2-pyrrolidone, 1-methyl-4-methoxycarbonyl-2-pyrrolidone, 1-lauryl-4-methoxycarbonyl-2-pyrrolidone, N-cyclohexylpyrrolidone, N-dimethylaminopropylpyrrolidone, N-cocoalkylpyrrolidone, N-tallowalkylpyrrolidone; biodegradable pyrrolidone derivatives, such as fatty acid esters of N-(2-hydroxyethyl)-2-pyrrolidone; cyclic amides, such as 1-dodecylazacycloheptan-2-one (Azone®), 1-geranylazacycloheptan-2-one, 1-farnesylazacycloheptan-2-one, 1-geranylgeranylazacycloheptan-2-one, 1-(3,7-dimethyloctyl)azacycloheptan-2-one, 1-(3,7,11-

trimethyldodecyl)azacycloheptan-2-one, 1-geranylazacyclohexane-2-one, 1-geranylazacyclopentan-2,5-dione, 1-farnesylazacyclopentan-2-one; hexamethylenelauramide and its derivatives; and diethanolamine and triethanolamine;

- various surfactants, such as anionic surfactants, including sodium laurate and sodium lauryl sulfate; cationic surfactants, including cetyltrimethyl ammonium bromide, tetradecyltrimethylammonium bromide, benzalkonium chloride, octadecyltrimethylammonium chloride, cetylpyridinium chloride, dodecyltrimethylammonium chloride, hexadecyltrimethylammonium chloride; nonionic surfactants, such as Polaxamer (231, 182, 184), Brij (30, 93, 96, 99), Span (20, 40, 60, 80, 85), Tween (20, 40, 60, 80), Myrj (45, 51, 52), Miglyol 840; various bile salts, such as sodium cholate, sodium salts of taurocholic, glycholic, desoxycholic acids; lecithin;
- various terpenes, including hydrocarbons, such as D-limonene,  $\alpha$ -pinene,  $\beta$ -carene; various terpene alcohols, including  $\alpha$ -Terpineol, terpinen-4-ol, carvol; various terpene ketones, including carvone, pulegone, piperitone, menthone; various terpene oxides, including cyclohexane oxide, limonene oxide,  $\alpha$ -pinene oxide, cyclopentene oxide, 1,8-cineole; various terpene oils, including ylang ylang, anise, chenopodium, eucalyptus;
- various alkanones, such as *N*-heptane, *N*-octane, *N*-nonane, *N*-decane, *N*-undecane, *N*-dodecane, *N*-tridecane, *N*-tetradecane, *N*-hexadecane;
- various organic acids, such as salicylic acid and salicylites (including their methyl, ethyl, and propyl glycol derivatives), citric and succinic acid.

In addition to the examples cited here, other topically-applicable formulations familiar to those of ordinary skill in the art, including various simple or complex combinations of vehicles and adjuvants, will be useful for improving delivery of the photoactive component of the medicament to target tissues. Background on such vehicles and adjuvants may be found, for example, in: E.W.

Smith and H.I. Maibach, "Percutaneous Penetration Enhancers: The Fundamentals"; S.C. Chattaraj and R.B. Walker, "Penetration Enhancer Classification"; and B.J. Aungst, "Fatty Acids as Skin Permeation Enhancers"; in E.W. Smith and H.I. Maibach (eds), Percutaneous Penetration Enhancers, CRC Press, Boca Raton, 1995. These references are incorporated herein by reference in their entirety.

5 Further, appropriate topically-applicable medicament formulations can, for example, incorporate various complex delivery vehicles, including various commercial vehicles, such as those available from Paddock Laboratories, including *Dermabase*®, *Hydrocream*, *Aquabase*, *Liquaderm-A*, *Liqua-Gel*, *Ora-Plus*®, *Ora-Sweet*® and *Ora-Sweet SF*, *Suspendol-S*, *Fattibase* and *Polybase*, as well as various proprietary vehicles, such as propylene glycol with one or more adjuvant delivery agent, so as to enhance delivery of the at least one halogenated xanthene or halogenated xanthene derivative to desired tissues to be treated. A comparison of the delivery properties for several example formulations is provided in Table 2, showing that both the quantity of active ingredient delivered to various tissues and the depth of such delivery beyond the application point can be substantially controlled by medicament formulation.

10  
15 2. Methods and medical use of the subject medicament for treatment of conditions affecting the skin and related organs.

The applicants have discovered that the medicaments disclosed herein are broadly applicable to improved treatment of various conditions affecting the skin and related organs of humans and animals. The medicament can be applied directly to, or substantially proximal to, tissues to be treated, including those of the skin, nails, scalp and oral cavity. Example indications include treatment for: Psoriasis and Pustular Psoriasis; Reiter's Syndrome; Skin Ulcers, including Stasis Dermatitis, Stasis Ulcers, Ischemic Ulcers, Sickle Cell Leg Ulcers, Diabetic Ulcers, Inflammatory Ulcers; Eczematous Disease and Eczematous Reaction; various Ichthyoses; Atopic Dermatitis; Superficial



Wrinkles; Near Surface Fat Reduction; Benign and Malignant Proliferative Disorders, such as Benign Epithelial Tumors and Hamartomas; Premalignant and Malignant Epithelial Tumors, including Actinic Keratoses, Basal Cell Carcinoma, Squamous Cell Carcinoma, and Keratoacanthoma; Benign and Malignant Adnexal Tumors; Tumors of Pigment-Producing Cells, including Malignant Melanoma, Solar Lentigines, Nevi, and Café-au-lait; Sarcomas; Lymphomas; Vascular Disorders, such as Hemangiomas and Port Wine Stain; Microbial Infection, such as Bacterial, Fungal, Yeast, Parasitic or Other Infections; Warts; and Acne.

In an example of a preferred embodiment of this method of treatment or medical use, applicants have found that application of a cream or solution containing Rose Bengal at a concentration of approximately 0.1% W/V to persistent leg ulcers, followed, after a latency period of 0-72 hours, and more preferably 0-1 hour, by illumination with approximately 10 to 200 J/cm<sup>2</sup> of continuous or pulsed green light in the 500-600 nm band, leads to substantial or complete healing of such persistent leg ulcers, with little or no side effects in surrounding tissue. The present invention, however, is not limited to this preferred embodiment, as other medicaments disclosed herein can also be used. Further, other formulations of the halogenated xanthenes as described herein have similar applications for the specific indications described herein, and for various other similar indications, including those related to therapeutic or cosmetic treatment of the skin and related organs of humans and animals.

### 3. Methods and medical use of the subject medicament for treatment of conditions affecting the mouth and digestive tract and related organs

The applicants have discovered that the medicaments disclosed herein are broadly applicable to improved treatment of various conditions affecting the mouth and digestive tract and related organs of humans and animals. The medicament can be applied directly to, or substantially proximal

to, tissues to be treated, including those of the mouth, gums, tongue, larynx, pharynx, esophagus, stomach, intestines and colon. Example indications include treatment for: Benign Esophageal Lesions, Barretts Esophagus and other Esophageal Hyperplasia and Dysplasia, and Esophageal Cancer, including Squamous Cell Carcinoma, Adenocarcinoma, Carsinosarcoma, Pseudosarcoma, and Sarcoma; Gastric Ulcers, Leiomyomas, Polyps, Neoplasms, Lymphoma and Pseudolymphoma, Adenocarcinoma, Primary Lymphoma, Leiomyosarcoma; Oral and Oropharynx Cancer and Premalignancies, Ulcers and Inflammatory Lesions, including Squamous Cell Carcinoma, Lymphoma, Actinic Cheilitis, Nicotine Stomatitis, Leukoplakia, Erythroplakia; Gum and Other Periodontal Disease, including Gingivitis; Laryngeal Hyperplasia, Dysplasia and Neoplasms; Colorectal Cancer and Polyps.

In an example of a preferred embodiment of this method of treatment or medical use, applicants have found that application of a solution containing Rose Bengal at a concentration of approximately 1% W/V in saline to esophageal tissue, followed, after a latency period of 0-72 hours, and more preferably 0-1 hour, by illumination with approximately 10 to 200 J/cm<sup>2</sup> of continuous or pulsed green light in the 500-600 nm band, leads to substantial or complete eradication of diseased tissues, such as those present in Barretts esophagus, with little or no side effects in surrounding tissue. The present invention, however, is not limited to this preferred embodiment, as other medicaments disclosed herein can also be used. Further, other formulations of the halogenated xanthenes as described herein have similar applications for the specific indications described herein, and for various other similar indications, including those related to therapeutic or cosmetic treatment of the mouth and digestive tract and related organs of humans and animals.

4. Methods and medical use of the subject medicament for treatment of conditions affecting the urinary and reproductive tracts and related organs.

The applicants have discovered that the medicaments disclosed herein are broadly applicable to improved treatment of various conditions affecting the urinary and reproductive tracts and related organs of humans and animals. The medicament can be applied directly to, or substantially proximal to, tissues to be treated, including those of the urethra, bladder, ureter, kidneys, vulva, vagina, cervix, fallopian tubes, ovaries, penis, testes, vas deferens, prostate, and epididymis. Example indications include treatment for: Urinary Tract Disease, including Cancerous and Pre-Cancerous Hyperplasia, Dysplasia and Neoplasms, Tumors and other Growths, Inflammation, and Infection of the Bladder, Ureter, Urethra, and Kidney; Cancerous and Pre-Cancerous Hyperplasia, Dysplasia and Neoplasms, Tumors and other Growths, Inflammation, and Infection of the Cervix, Endometrium, Myometrium, Ovaries, Fallopian Tubes, Uterus, Vulva, and Vagina; Cancerous and Pre-Cancerous Hyperplasia, Dysplasia and Neoplasms, Tumors and other Growths, Inflammation, and Infection of the Prostate and Testes; Reproductive Tract Infections, including Tinea Cruris, Candidiasis, Condylomata Acuminata, Molluscum Contagiosum, Genital Herpes Simplex Infection, Lymphogranuloma Venereum, Chancroid, Granuloma Inguinale, Erythrasma; Psoriasis; and Lichen Planus and Lichen Sclerosus.

In an example of a preferred embodiment of this method of treatment or medical use, applicants have found that application of a solution containing Rose Bengal at a concentration of approximately 1% W/V to tissue, followed, after a latency period of 0-72 hours, and more preferably 0-1 hour, by illumination with approximately 10 to 200 J/cm<sup>2</sup> of continuous or pulsed green light in the 500-600 nm band, leads to substantial or complete eradication of diseased tissues, such as those present in bladder tumors, with little or no side effects in surrounding tissue. The present invention, however, is not limited to this preferred embodiment, as other medicaments disclosed herein can also

be used. Further, other formulations of the halogenated xanthenes as described herein have similar applications for the specific indications described herein, and for various other similar indications, including those related to therapeutic or cosmetic treatment of the urinary and reproductive tracts and related organs of humans and animals.

5

5. Methods and medical use of the subject medicament for treatment of conditions affecting the respiratory tract and related organs.

The applicants have discovered that the medicaments disclosed herein are broadly applicable to improved treatment of various conditions affecting the respiratory tract and related organs of humans and animals. The medicament can be applied directly to, or substantially proximal to, tissues to be treated. Example indications include treatment for: Hyperplasia, Dysplasia and Neoplasia, Cancer, Inflammation and Infection of the Nasal Cavity, Paranasal Sinuses, Tear Ducts, Eustachian Tubes, Nasopharynx, Hypopharynx, Larynx, Trachea, Bronchi, Lung and Alveoli.

In an example of a preferred embodiment of this method of treatment or medical use, applicants have found that application of a solution containing Rose Bengal at a concentration of approximately 1% W/V to tissue, followed, after a latency period of 0-72 hours, and more preferably 0-1 hour, by illumination with approximately 10 to 200 J/cm<sup>2</sup> of continuous or pulsed green light in the 500-600 nm band, leads to substantial or complete eradication of diseased tissues, such as those present in tracheal tumors, with little or no side effects in surrounding tissue. The present invention, however, is not limited to this preferred embodiment, as other medicaments disclosed herein can also be used. Further, other formulations of the halogenated xanthenes as described herein have similar applications for the specific indications described herein, and for various other similar indications, including those related to therapeutic or cosmetic treatment of the respiratory tracts and related organs of humans and animals.

6. Methods and medical use of the subject medicament for treatment of conditions affecting various other internal or external tissue surfaces, such as tissue surfaces exposed during surgery.

The applicants have discovered that the medicaments disclosed herein are broadly applicable to improved treatment of various conditions affecting various other internal or external tissue surfaces of humans or animals, such as tissue surfaces exposed during surgery, including endoscopic surgery or other endoscopic procedures. The medicament can be applied directly to, or substantially proximal to, tissues to be treated. Example indications include treatment for: Joint Inflammation, such as that of Arthritis; Resected Tumor Beds of Intra-cranial and other Head and Neck, Thoracic, or Abdominal Tumors; Cardiac and Pericardial Tissues and Circulatory Tissues, including Arteries and Veins, including Plaques and Infections of such tissues, such as Bacterial Endocarditis; Metastatic Tumors, such as Metastases of Breast Tumors to the Skin; and various other substantially similar indications.

In an example of a preferred embodiment of this method of treatment or medical use, applicants have found that application of an aqueous solution containing Rose Bengal at a concentration of approximately 10 % W/V micromolar to breast adenocarcinoma and sarcoid tissues, followed, after a latency period of 0-72 hours, and more preferably 0-1 hour, by illumination with approximately 10 to 200 J/cm<sup>2</sup> of continuous or pulsed green light in the 500-600 nm band, leads to substantial or complete eradication of such tissues, with little or no side effects in surrounding tissue. The present invention, however, is not limited to this preferred embodiment, as other medicaments disclosed herein can also be used. Further, other formulations of the halogenated xanthenes as described herein have similar applications for the specific indications described herein, and for various other similar indications, including those related to therapeutic or cosmetic treatment of various other internal or external tissue surfaces of humans or animals, such as tissue surfaces exposed during surgery.

7. Methods and medical use of the subject medicament for treatment of conditions related to microbial or parasitic infection.

The applicants have discovered that the medicaments disclosed herein are broadly applicable to improved treatment of various conditions related to microbial or parasitic infection of humans or animals, including those infections resistant to conventional treatments. The medicament can be applied directly to, or substantially proximal to, tissues to be treated. Example indications include treatment for: Bacterial and Antibiotic Resistant Bacterial Infection, including those caused by Gram Positives and Gram Negatives, Streptomyces, Actinomyces, Staphylococci, Streptococci, Pseudomonas, Escherichia coli, Mycobacteria and others; Infection caused by Filamentous Fungi and Non-filamentous Fungi like Cryptosporidium, Histoplasma, Aspergillus, Blastomyces, Candida and others; Parasitic Infection caused by Amoeba (including for use in lysing and killing amoeba in amoebic cysts), Trichinella, Dirofilaria (Heart worm in dogs) and others.

In an example of a preferred embodiment of this method of treatment or medical use, applicants have found that application of an aqueous solution containing Rose Bengal at a concentration of approximately 1 to 10 micromolar or greater to antibiotic resistant Staphylococcus aureus, Escherichia coli, various other gram positive and gram negative bacteria, and various yeasts, followed, after a latency period of 0-72 hours, and more preferably 0-1 hour, by illumination with approximately 10 to 200 J/cm<sup>2</sup> of continuous or pulsed green light in the 500-600 nm band, leads to substantial or complete eradication of such microbes, with little or no side effects in surrounding tissue. The present invention, however, is not limited to this preferred embodiment, as other medicaments disclosed herein can also be used. Further, other formulations of the halogenated xanthenes as described herein have similar applications for the specific indications described herein, and for various other similar indications, including those related to therapeutic or cosmetic treatment of various other conditions related to microbial or parasitic infection of humans or animals.

Table 1. Chemical, Physical and Photochemical Properties of Some Example Halogenated Xanthenes:

Compound	Substitution					MW (g)	$\lambda_{max}$ (nm)			$\alpha$ ( $\text{cm}^{-1} \cdot \text{mol}^{-1} \cdot \text{L}$ )	$\phi$ (singlet oxygen)		
	X	Y	Z	R <sup>1</sup>	R <sup>2</sup>		H <sub>2</sub> O	EtOH	MeOH		MeOH	EtOH	MeOH
Fluorescein	H	H	H	Na	Na	376	490	499	492	$6.4 \times 10^4$	0.03	0.03	0.09
4',5'-Dichlorofluorescein	Cl	H	H	Na	Na	445	502	511			0.04	0.07	
2',7'-Dichlorofluorescein	H	Cl	H	Na	Na	445	502	511			0.04	0.07	
4,5,6,7-Tetrachlorofluorescein	H	H	Cl	H	H	470	515			$2.9 \times 10^4$			
2',4',5',7'-Tetrachlorofluorescein	Cl	Cl	H	Na	Na	514	510	520			0.05	0.05	
Dibromofluorescein	Br	H	H	Na	Na	534	504	510		$1.4 \times 10^4$	0.32	0.42	
Solvent Red 72	H	Br	H	H	H	490			450	$1.4 \times 10^4$			
Diiodofluorescein	I	H	H	Na	Na	628	506	513		$5.8 \times 10^4$	0.33	0.48	
Eosin B	NO <sub>2</sub>	Br	H	Na	Na	624	522			$3.9 \times 10^4$			
Eosin Y	Br	Br	H	Na	Na	692	517	523	527	$9.1 \times 10^4$	0.28	0.57	0.39
Ethyl Eosin	Br	Br	H	C <sub>2</sub> H <sub>5</sub>	K	714		532		$1.1 \times 10^4$			
Erythrosin B	I	I	H	Na	Na	880	528	532	529	$9.1 \times 10^4$	0.62	0.63	0.62
Phloxine B	Br	Br	Cl	Na	Na	830	541	548	547	$1.0 \times 10^5$	0.40	0.63	
Rose Bengal	I	I	Cl	Na	Na	1018	547	557	556	$1.0 \times 10^5$	0.76	0.75	0.76
Rose Bengal Dilithium	I	I	Cl	Li	Li	986		559					
Rose Bengal Amide	I	I	Cl	C <sub>2</sub> H <sub>5</sub>	(C <sub>2</sub> H <sub>4</sub> ) <sub>3</sub> NH	1100		563					0.74
Rose Bengal Diamide	I	I	Cl	(C <sub>2</sub> H <sub>5</sub> ) <sub>3</sub> NH	(C <sub>2</sub> H <sub>4</sub> ) <sub>3</sub> NH	1166		559					0.72
4,5,6,7-Tetrabromoerythrosin	I	I	Br	Na	Na	1195							

**Table 2.** Relative delivery efficacy of example transdermal delivery formulations of a halogenated xanthene; Rose Bengal is used as the agent at concentrations indicated by [RB]. The Formulation is applied to murine skin for 30 minutes under occlusive conditions. The Relative Efficacy indicates an estimate of the quantity of Rose Bengal delivered into the tissue, based on fluorescence measurement at the surface and in tissue cross sections. Depth indicates the relative depth of Rose Bengal penetration: LP = penetration to lamina propria; D+ = penetration to dermis and beyond.

Formulation			Relative Efficacy	Depth
[RB]	Vehicle	Adjuvant		
1%	Water	NaCl, 0.9%	HIGH	LP
1%	Propylene Glycol	none	LOW	LP
1%	Propylene Glycol	Lauric Acid, 5%	MED-HIGH	LP
1%	Propylene Glycol	Oleic Acid, 5%	MED	LP
1%	Propylene Glycol	Linoleic Acid, 5%	MED-LOW	LP
1%	DMSO	none	VERY HIGH	D+
1%	Liquaderm-A	none	LOW	LP
1%	Liqua-Gel	none	MED-HIGH	LP

This description has been offered for illustrative purposes only and is not intended to limit the invention of this application, which is defined in the claims below.

What is claimed as new and desired to be protected by Letters Patent is set forth in the appended claims.



## CLAIMS:

We claim:

1. A medicament for topical application, the medicament comprising at least one halogenated xanthene as a primary active component, wherein said medicament is useful for photodynamic treatment of human and animal tissue.

2. The medicament of Claim 1 wherein said halogenated xanthene is present in a concentration of greater than 0.001% to less than 20%.

3. The medicament of Claim 1 wherein said halogenated xanthene comprises Rose Bengal.

4. The medicament of Claim 1 wherein said halogenated xanthene includes at least one compound selected from the group consisting of Fluorescein; 4',5'-Dichlorofluorescein; 2',7'-Dichlorofluorescein; 4,5,6,7-Tetrachlorofluorescein; 2',4',5',7'-Tetrachlorofluorescein; Dibromofluorescein; Solvent Red 72; Diiodofluorescein; Eosin B; Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Trifluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein.

5. The medicament of Claim 1 further comprising at least one targeting moiety coupled to said halogenated xanthene.

6. The medicament of Claim 5 wherein said targeting moiety is selected from the group consisting of DNA, RNA, amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors or complexing agents, lipid receptors or complexing agents, protein receptors or complexing agents, chelators, encapsulating vehicles, short- or long-chain aliphatic or aromatic hydrocarbons, aldehydes, ketones, alcohols, esters, amides, amines, nitriles, azides, and other hydrophilic or hydrophobic moieties.

7. The medicament of Claim 1 wherein said medicament is formulated in a delivery vehicle selected from the group consisting of liquids, semisolids, solids and aerosols

8. The medicament of Claim 8 wherein said vehicle is selected from the group consisting of aqueous, non-aqueous and nanoparticulate suspensions, solutions, creams, ointments, gels, syrups, suppositories and micro-droplet sprays.

9. The medicament of Claim 1 wherein said halogenated xanthene is in a delivery vehicle that includes an adjuvant selected from the group consisting of builders, stabilizers, emulsifiers, dispersants, preservatives, buffers, electrolytes, tissue penetrating agents and tissue softening agents.

10. The medicament of Claim 1 wherein said medicament is useful for the treatment of indications selected from the group consisting of conditions affecting the skin and related organs, conditions affecting the mouth and digestive tract and related organs, conditions affecting the urinary and reproductive tracts and related organs, conditions affecting the respiratory tracts and related

organs, conditions affecting other internal and external tissue surfaces, conditions affecting tissue surfaces exposed during surgery, and conditions related to microbial or parasitic infection.

11. The medicament of Claim 1 wherein said medicament is useful for photodynamic  
5 treatment using a green activating light.

12. The method of Claim 11 wherein said green light has a wavelength of between approximately 500 nm and 600 nm.

13. Use of a halogenated xanthene in the preparation of a topical medicament for  
10 treatment of human and animal tissue using photodynamic therapy.

14. The use of Claim 13 for preparation of a medicament for the treatment of indications  
15 selected from the group consisting of conditions affecting the skin and related organs, conditions affecting the mouth and digestive tract and related organs, conditions affecting the urinary and reproductive tracts and related organs, conditions affecting the respiratory tracts and related organs, conditions affecting other internal and external tissue surfaces, conditions affecting tissue surfaces exposed during surgery, and conditions related to microbial or parasitic infection.

20 15. The use of Claim 13 wherein said halogenated xanthene comprises Rose Bengal.

16. The use of Claim 13 wherein said medicament is for photodynamic therapy with green activating light.

17. Use of a halogenated xanthene comprising:

administering a therapeutically effective amount of a halogenated xanthene to or proximate to human or animal tissue and photoactivating the halogenated xanthene present within or proximate to said tissue.

5

18. The use of Claim 17 wherein said halogenated xanthene comprises Rose Bengal.

19. The use of Claim 17 wherein said halogenated xanthene is photoactivated with green activating light.

20. The use of Claim 19 wherein said green light has a wavelength of between approximately 500 nm and 600 nm.

21. A pharmaceutical composition for topical administration comprising a halogenated xanthene for treatment using photodynamic therapy.

22. The pharmaceutical composition of Claim 21 wherein said halogenated xanthene is present in a concentration of greater than 0.001% to less than 20%.

23. The pharmaceutical composition of Claim 21 wherein said halogenated xanthene comprises Rose Bengal.

24. The pharmaceutical composition of Claim 21 wherein said halogenated xanthene includes at least one compound selected from the group consisting of Fluorescein; 4',5'-Dichlorofluorescein; 2',7'-Dichlorofluorescein; 4,5,6,7-Tetrachlorofluorescein; 2',4',5',7'-Tetrachlorofluorescein; Dibromofluorescein; Solvent Red 72; Diiodofluorescein; Eosin B; Eosin Y; Ethyl Eosin; Erythrosin B; Phloxine B; Rose Bengal; 4,5,6,7-Tetrabromoerythrosin; Mono-, Di-, or Tribromoerythrosin; Mono-, Di-, or Trichloroerythrosin; Mono-, Di-, or Tricfluoroerythrosin; 2',7'-Dichloro-4,5,6,7-Tetrafluorofluorescein; 2',4,5,6,7,7'-Hexafluorofluorescein; and 4,5,6,7-Tetrafluorofluorescein.

25. The pharmaceutical composition of Claim 21 further comprising at least one targeting moiety coupled to said halogenated xanthene.

26. The pharmaceutical composition of Claim 25 wherein said targeting moiety is selected from the group consisting of DNA, RNA, amino acids, proteins, antibodies, ligands, haptens, carbohydrate receptors or complexing agents, lipid receptors or complexing agents, protein receptors or complexing agents, chelators, encapsulating vehicles, short- or long-chain aliphatic or aromatic hydrocarbons, aldehydes, ketones, alcohols, esters, amides, amines, nitriles, azides, and other hydrophilic or hydrophobic moieties.

27. The pharmaceutical composition of Claim 21 wherein said pharmaceutical composition is formulated in a delivery vehicle selected from the group consisting of liquids, semisolids, solids and aerosols

28. The pharmaceutical composition of Claim 27 wherein said vehicle is selected from the group consisting of aqueous, non-aqueous and nanoparticulate suspensions, solutions, creams, ointments, gels, syrups, suppositories and micro-droplet sprays.

5 29. The pharmaceutical composition of Claim 21 wherein said halogenated xanthene is in a delivery vehicle that includes an adjuvant selected from the group consisting of builders, stabilizers, emulsifiers, dispersants, preservatives, buffers, electrolytes, tissue penetrating agents and tissue softening agents.

10 30. The pharmaceutical composition of Claim 21 wherein said photodynamic therapy uses green activating light.

31. The pharmaceutical composition of Claim 30 wherein said green light has a wavelength of between approximately 500 and 600 nm.

15 32. A method of treating comprising:  
topically applying a medicament including at least one halogenated xanthene to or proximate to human or animal tissue; and  
illuminating said human or animal tissue to activate said halogenated xanthene present within  
20 or proximate to said tissue.

33. The method of Claim 32 wherein said human or animal tissue comprises the skin and related organs, the mouth and digestive tract and related organs, the urinary and reproductive tracts

and related organs, the respiratory tracts and related organs, other internal and external tissue surfaces, tissue surfaces exposed during surgery, and tissue with microbial or parasitic infection.

34. The method of Claim 32 wherein said step of illuminating uses green activating light.

5

35. The method of Claim 34 wherein said green light has a wavelength of between approximately 500 and 600 nm.

36. A topically-applicable medicament comprising at least one halogenated xanthene as a primary active component, wherein such medicament is useful for photodynamic treatment of human and animal tissue.

37. A topically-applicable medicament comprising at least one halogenated xanthene as a primary active component, wherein such medicament is useful for indications selected from the group consisting of conditions affecting the skin and related organs, conditions affecting the mouth and digestive tract and related organs, conditions affecting the urinary and reproductive tracts and related organs, conditions affecting the respiratory tracts and related organs, other conditions affecting internal and external tissue surfaces, conditions affecting tissue surfaces exposed during surgery, and conditions related to microbial or parasitic infection.

20

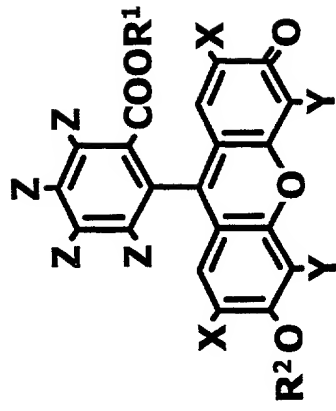
## **ABSTRACT OF DISCLOSURE**

New photodynamic, topically-applicable medicaments and certain medical uses of such photodynamic medicaments for treatment of human or animal tissue are described, wherein a primary  
5 active component of such medicaments is a halogenated xanthene. The halogenated xanthenes constitute a family of potent photosensitizers that become photoactivated upon illumination of the treatment site with visible wavelengths of light. In preferred embodiments, such medicaments are used for treatment of a variety of conditions affecting the skin and related organs; the mouth and digestive tract and related organs; the urinary and reproductive tracts and related organs; the  
10 respiratory tract and related organs; various other internal or external tissue surfaces, such as tissue surfaces exposed during surgery; and for treatment of a variety of conditions related to microbial or parasitic infection. In another preferred embodiment, such medicaments are produced in various formulations including liquid, semisolid or aerosol delivery vehicles.

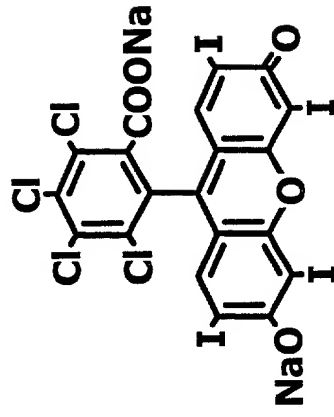




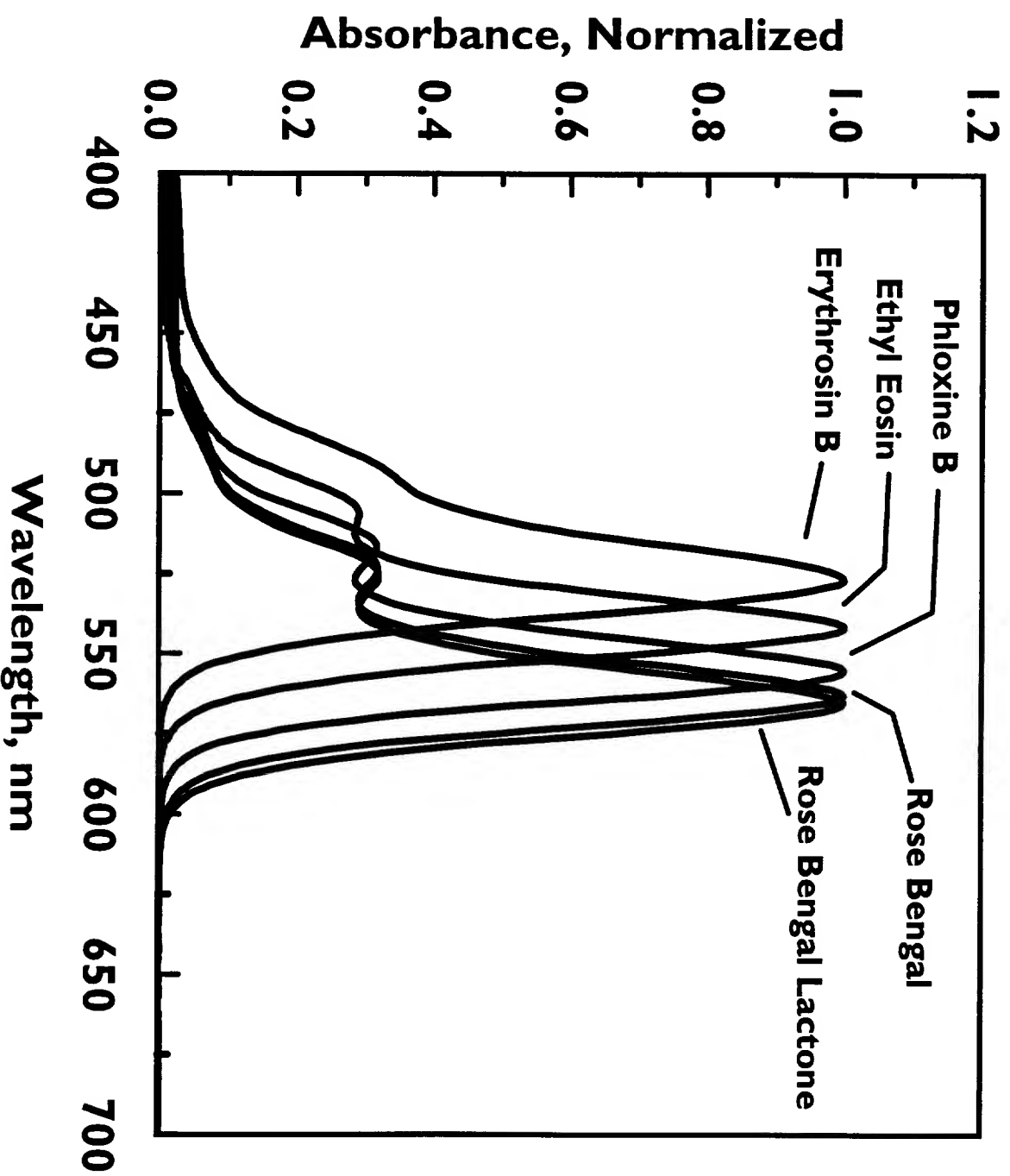
**Fig. 1a**



**Fig. 1b**



**Fig. 2**



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

H. Craig DEES et al

Serial No.: Not Assigned

Filed: Herewith

For: IMPROVED TOPICAL MEDICAMENTS AND  
METHODS FOR PHOTODYNAMIC TREATMENT  
OF DISEASE

To:

Assistant Commissioner for Patents  
Washington D.C. 20231

) EL613562139  
) "Express Mail" Mailing Label No. \_\_\_\_\_  
) Date of Deposit August 9, 2000  
)  
) I hereby certify that this paper or fee is being  
) deposited with the United States Postal Service  
) "Express Mail Post Office to Addressee" service  
) under 37 CFR 1.10 on the date indicated above  
) and is addressed to the Assistant Commissioner  
) for Patents, Washington, D.C. 20231.  
)  
) Name ARMANDO CHING  
) (typed or printed)

Signature Armando Ching

APPOINTMENT OF ASSOCIATE ATTORNEYS

Sir:

Please recognize the following as my associate attorneys in  
the above captioned application:

Fred S. Lockwood	Reg. No. 14,772
Granger Cook, Jr.	Reg. No. 18,283
William H. Magidson	Reg. No. 19,902
John L. Alex	Reg. No. 22,017
Daniel M. Riess	Reg. No. 24,375
Eugene M. Cummings	Reg. No. 24,398
Raymond M. Mehler	Reg. No. 26,306
Gary W. McFarron	Reg. No. 27,357
Stephen B. Heller	Reg. No. 30,181
David Lesht	Reg. No. 30,472
Andrew G. Kolomayets	Reg. No. 33,723
Mark J. Murphy	Reg. No. 34,225
David M. Mundt	Reg. No. 41,207
John R. Lagowski	Reg. No. 41,922
Michael J. McGee	Reg. No. 43,789

Respectfully submitted,

Edward D. Manzo

Edward D. Manzo  
Attorney of Record  
Registration No. 28,139

COOK, ALEX, MCFARRON, MANZO,  
CUMMINGS & MEHLER, LTD.  
200 West Adams Street, Suite 2850  
Chicago, Illinois 60606  
(312) 236-8500